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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Heparin-Induced Thrombocytopenia

A Comprehensive Clinical Review

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ABSTRACT

Heparin-induced thrombocytopenia is a profoundly dangerous, potentially lethal, immunologically mediated adverse drug reaction to unfractionated heparin or, less commonly, to low-molecular weight heparin. In this comprehensive review, the authors highlight heparin-induced thrombocytopenia's risk factors, clinical presentation, pathophysiology, diagnostic principles, and treatment. The authors place special emphasis on the management of patients requiring procedures using cardiopulmonary bypass or interventions in the catheterization laboratory. Clinical vigilance of this disease process is important to ensure its recognition, diagnosis, and treatment. Misdiagnosis of the syndrome, as well as misunderstanding of the disease process, continues to contribute to its morbidity and mortality.
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Unfractionated heparin (UFH) and other heparin derivatives, such as low-molecular weight heparin (LMWH), are among the most frequently prescribed medications worldwide (1). They are routinely used for therapeutic and prophylactic anticoagulation in a multitude of medical and surgical conditions (2). Although hemorrhagic events are the most common complication of heparin therapy, thrombotic complications are also possible in patients who develop heparin-induced thrombocytopenia (HIT) (3). Mortality associated with HIT is reported at between 20% and 30% (4,5).

HIT is a dangerous, potentially lethal, immunologically mediated adverse drug reaction to UFH or, less commonly, to LMWH (6,7). An older nomenclature defined 2 types of HIT: type I and type II (8). Type I, seen in 10% to 30% of patients given heparin, was characterized by a benign, mild thrombocytopenia occurring in the first 2 days after heparin administration (9). Platelet count spontaneously normalizes, even with continued heparin therapy, and is not associated with increased thrombotic risk (10–12). Type II refers to the antibody-mediated, potentially fatal disorder, now referred to as HIT, in which heparin therapy needs to be discontinued as soon as the diagnosis is suspected (10,13,14). It also requires the implementation of an alternative anticoagulation strategy to prevent the development of HIT with thrombosis (HITT) (15).

In this comprehensive review, we highlight HIT's risk factors, clinical presentation, pathophysiology, diagnostic principles, and treatment. We place special emphasis on the management of patients requiring procedures using cardiopulmonary bypass (CPB) or interventions in the catheterization laboratory. Increased awareness of this condition among clinicians is important to ensure its early recognition and treatment, to avoid serious complications (1). Misdiagnosis of the syndrome, as well as misunderstanding of the disease process, continues to contribute to its morbidity and mortality (11).

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ABBREVIATIONS AND ACRONYMS

ACCP = American College of Chest Physicians

ACT = activated clotting time

aPTT = activated partial thromboplastin time

CPB = cardiopulmonary bypass

DTI = direct thrombin inhibitor

ECT = ecarin clotting time

ELISA = enzyme-linked immunosorbent assay

FDA = U.S. Food and Drug Administration

HIT = heparin-induced thrombocytopenia

HITT = heparin-induced thrombocytopenia with thrombosis

IgG = immunoglobulin G

INR = international normalized ratio

LMWH = low-molecular weight heparin

PCI = percutaneous coronary intervention

PF4 = platelet factor 4

UFH = unfractionated heparin

INCIDENCE, EPIDEMIOLOGY, AND RISK FACTORS

Studies indicate that the prevalence of HIT ranges from 0.1% to 5.0% in patients receiving heparin (3,8,16,17), with about 25% to 50% of these patients developing HITT (9,18). The risk for developing HIT varies considerably according to several patient- and drug-related factors (3,8,16). The parameters most strongly associated with an increased risk for the development of HIT are: 1) the duration of heparin therapy; 2) the type and dose of heparin administered; 3) the indication for treatment; and 4) the patient's sex.

Prolonged exposure to heparin therapy (>5 days) has been shown to be a frequent risk factor for developing thrombocytopenia and the further development of HIT (19–21). UFH conveys a risk 10 times greater than that of LMWH (22–26), whereas the pentasaccharide fondaparinux is rarely associated with HIT, having been described in only a few case reports (27,28). Also, the origin of heparin affects the risk, with bovine UFH associated with a higher risk than porcine UFH (19,29). Therapeutic anticoagulation doses frequently result in greater platelet reductions; in HIT, however, even exposure to very small amounts of heparin (heparin flushes) can lead to the formation of HIT antibodies (21,30).

With regard to the indication for heparinization, surgical (particularly cardiac and orthopedic) or trauma patients (1% to 5%) have a far greater risk than medical or intensive care unit patients (<1%) for the development of HIT (31,32).

And finally, female patients have approximately twice the risk for developing HIT, often attributed to their increased immune responses (19,20,22,23,26,33,34).

CLINICAL PRESENTATION

The main clinical presentation of HIT is thrombocytopenia. After heparin exposure, platelet numbers decline rapidly, sometimes by 50% or more from baseline. Platelet counts fall below 150×10^9/l in 90% of patients, with a median nadir of about 55×10^9/l (35). There are 3 patterns of onset for HIT: rapid, typical, and delayed. Sixty percent of patients with HIT exhibit the typical pattern, resulting in a platelet decline 5 to 10 days after exposure. In 30% of cases, the onset pattern is rapid, where platelet numbers decline immediately post-exposure (4,35). Such a robust response can be the result of previous exposure to heparin in the past 100 days and residual antibody presence from heparin sensitization (35). Last, the remaining patients exhibit delayed-onset HIT, occurring an average of 9.2 days after initiating therapy; however, signs and symptoms can appear up to 3 weeks post-exposure (35).

Frequently, post-surgical patients exhibit a unique bimodal pattern of platelet decline. Initially, they may develop thrombocytopenia on post-operative day 1, but this usually rebounds in 5 to 6 days (36–38). A second decline in platelet count is more likely to be associated with HIT and should warrant further investigation (23,37–40). Importantly, clinicians should use the new, post-operative platelet count as a baseline.

Although HIT is characterized by thrombocytopenia, the disease process results in a paradoxical, prothrombotic disorder, with an incidence of thrombosis ranging from 50% to 89% in untreated patients (1,4,6,23,41). It can lead to devastating arterial and venous thromboembolic complications, including pulmonary embolism, mesenteric ischemia, ischemic limb necrosis, acute myocardial infarction, and stroke (5,6,8,42). Venous thromboses predominate over arterial thromboses in medical patients with HIT or following orthopedic surgery (40), whereas arterial and venous thromboses occur with similar frequency following vascular and cardiac surgery in patients with HIT (7). Additionally, 10% to 20% of patients have localized skin necrosis at heparin injection sites (4,5), and up to 20% of patients can develop disseminated intravascular coagulation (43).

However, when the clinical picture includes thrombocytopenia, it is important to review the multiple scenarios that should be included in the differential diagnosis. These disease processes include acute pulmonary embolism, end-stage renal disease, sepsis, and patients with recent CPB, indwelling arterial devices (e.g. intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation), and medications (4,44).

CLINICAL SCORING SYSTEMS

The diagnosis of HIT involves both clinical and laboratory components; thus, there are several proposed scoring systems to predict the likelihood of HIT by clinical characteristics. They include the HIT Expert Probability Score by Cuker et al. (36), a post-CPB scoring system by Lillo-Le Louët et al. (39), and the commonly used 4 T's scoring system by Warkentin et al. (45,46).

TABLE 1 Post-CPB Scoring System

Variable	Clinical Scenario	Points
Platelet count	Pattern A (platelet count begins to recover after CPB but then begins to fall again >4 days after CPB)	2
	Pattern B (thrombocytopenia occurs immediately after CPB and persists for >4 days without recovery)	1
Time from CPB to index date	≥5 days	2
	<5 days	0
CPB duration	≤118 min	1
	>118 min	0

Total score: ≥2 points = high probability of HIT, <2 points = low probability of HIT. Reprinted with permission from Lillo-Le Louët et al. (39).

CPB = cardiopulmonary bypass; HIT = heparin-induced thrombocytopenia.

The first scoring system is the HIT Expert Probability Score (36), which uses 26 experts' opinions of the importance of various diagnostic characteristics associated with HIT. Although the HIT Expert Probability Score is promising (100% sensitivity, 60% specificity), the information needed to complete the score may not always be readily available, and the proposed results warrant validation in larger prospective studies. The second clinical scoring system, by Lillo-Le Louët et al. (39) (**Table 1**), is specific for the post-CPB population and assesses the timing of platelet decline and CPB duration. Reports suggest a negative predictive value of 97%; however, this probability model was developed retrospectively, has not been validated in prospective trials, and cannot be applied to nonsurgical patients.

The widely used 4 T's clinical scoring system evaluates the following 4 criteria (**Table 2**): 1) the degree of thrombocytopenia; 2) the timing of platelet decline after heparin administration; 3) the presence of thrombosis or other HIT sequelae; and 4) the probability of other causes of thrombocytopenia (45,46). Each category receives a score of 0 to 2, and the resulting total score places patients at low, intermediate, or high pre-test risk for having HIT. The 4 T's system has a high negative predictive value and is our preferred method of excluding HIT (41), as the probability of a true diagnosis in patients with low scores is low (47). However, the positive predictive value (10% to 20% for an intermediate score of 4 to 5 points, 40% to 80% for a high score of 6 to 8 points) is less reliable and more contingent on the clinician evaluating the patient. Thus, an intermediate or high score should prompt laboratory testing, further investigation, and possible alternate anticoagulation (45,47,48).

PATHOPHYSIOLOGY OF HIT

The pathophysiology of HIT involves the formation of a heparin/platelet factor (PF)-4 complex and the subsequent binding of immunoglobulin G (IgG) antibodies over 4 to 14 days (49). Although several other antibodies, including immunoglobulin M and immunoglobulin A, have been associated with HIT, their clinical relevance is minor or uncertain (50,51). IgG antibodies recognize neoepitopes on PF4 (within the polyanion/PF4 complex) and activate monocytes and platelets via their cellular FcγRIIa receptors (48,52). Consequently, this activation results in the generation of thrombin, tissue factor, platelet-fibrin thrombi, procoagulant microparticles, and the further release of PF4 (8,16,44,49).

The duration of this process is due to the required maturation of precursor B cells becoming plasma cells, which, in turn, excrete large amounts of monoclonal antibodies. The target antigen implicated

TABLE 2 The 4 T's Clinical Scoring System

Category	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count falls >50% and platelet nadir ≥20 × 10^9/l	Platelet count falls 30%–50% and platelet nadir 10–19 × 10^9/l	Platelet count falls <30% and platelet nadir <10 × 10^9/l
Timing	Clear onset between 5 and 10 days or platelet fall ≤1 day (prior heparin exposure within 30 day)	Consistent with days 5–10 fall, but not clear (e.g., missing platelet counts), or onset after day 10, or fall ≤1 day (prior heparin exposure 30–100 days ago)	Platelet count fall <4 days without recent heparin exposure
Thrombosis	New thrombosis (confirmed), or skin necrosis at heparin injection sites, or acute systemic reaction after intravenous heparin bolus	Progressive or recurrent thrombosis, or non-necrotizing (erythematous) skin lesions, or suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	Nonapparent	Possible	Definite

Probability of HIT: high, 6 to 8 points (21.4% to 100%); intermediate, 4 or 5 points (7.9% to 28.6%); low, 0 to 3 points (0% to 1.6%). Reprinted with permission from Lo et al. (45).

HIT = heparin-induced thrombocytopenia.

in the HIT process is a complex of heparin and PF4, a positively charged protein synthesized by megakaryocytes and stored in platelet alpha granules (44,53). Normally, plasma contains only trace levels of PF4, but the concentration can be increased 15- to 30-fold in the presence of a heparin infusion (40,44). In addition, elevated PF4 levels are seen in several different patient populations, including those with infection, diabetes, or renal disease, or in response to trauma or CPB (54).

LABORATORY STUDIES

It is important to remember that laboratory studies are necessary if a clinician (i.e., clinical scoring system) is suspicious for a diagnosis of HIT. Currently, the 2 classes of tests used to assist in the diagnosis of HIT are immunologic (antigenic) and functional (platelet activation) assays. Overall, these tests identify different steps along the pathogenesis of HIT: the antigen assay detects the initial immune response, whereas the functional assay detects the activation of platelets, leading to thrombosis.

Immunologic assays, such as the enzyme-linked immunosorbent assay (ELISA), have a high degree of sensitivity (99%) (55) and thus have high negative predictive value, making them excellent tests to rule out a diagnosis of HIT. However, by detecting less pathological immunoglobulins (immunoglobulin A and immunoglobulin M), false positives result in lower specificity (40,55). This is important for cardiovascular surgery patients, who occasionally test positive on ELISA but are rarely diagnosed with HIT (33,40,56). Additionally, there may be non-IgG-mediated proteins (such as neutrophil-activating peptide-2 or interleukin-8) involved in HIT that will not be detected by ELISA (51,57).

There are several recommended ways to increase the specificity and positive predictive value of immunologic assays. First, patients with high clinical suspicion of HIT should be explicitly tested for IgG, as it is the most clinically significant antibody (58–61). Second, the degree of reactivity on immunoassay, designated by optical density, should guide diagnosis and treatment (62–64). Studies have shown that higher overall optical density scores are more often associated with a positive serotonin release assay (63) and with higher risk for thrombosis (65–68). Furthermore, repeating the ELISA using 2-point testing (discussed later) increases the specificity of HIT testing (69,70) but can decrease the negative predictive value and sensitivity (71).

The diagnostic approach to HIT is further enhanced by combining the results of immunologic testing with a functional (platelet activation) assay (48). These tests measure platelet activation from the heparin-PF4-antibody complex by mixing donor platelet-rich plasma with patient plasma and heparin. The overall specificity increases by exposing samples to both therapeutic and supratherapeutic levels of heparin (2-point testing) and by using washed platelets (as opposed to platelet-rich plasma) (40,72,73). The 2 most common functional assays are the heparin-induced platelet activation assay and the serotonin release assay.

The heparin-induced platelet activation assay will exhibit platelet aggregation and an increase in turbidity at therapeutic concentrations of heparin, but not at supratherapeutic concentrations (74,75). The serotonin release assay, generally considered the gold standard because of its high sensitivity (>95%) and specificity (>95%) (73), measures the sample's radioactivity and the percentage release of serotonin from platelets (74).

Because the functional assays are time consuming, are expensive, and can require outside laboratory assistance, ELISA is usually the initial test in the diagnosis of HIT (6). Recently however, Mullier et al. (76) developed the platelet microparticle generation assay to minimize the radioactivity and difficulty of performing the serotonin release assay. Although early studies are very promising, it seems that more investigation needs to be undertaken (72,76).

Overall, the clinical suspicion and HIT probability (as determined by a clinical scoring system) will direct the approach to diagnosing HIT. Usually, patients with low probability scores are safe to continue receiving heparin therapy. Intermediate or greater probability scores merit further testing by immunologic assay and even consideration for alternate anticoagulation if suspicion is high. A negative immunologic assay in intermediate-risk patients effectively eliminates the diagnosis of HIT. It is very rare for a patient with high clinical suspicion to have a negative antibody test result, especially when using methods to increase specificity. These cases, along with any patient with a positive immunologic test result, warrant further confirmation using a functional platelet assay.

MANAGEMENT AND TREATMENT

CESSATION OF THERAPY. It is of paramount importance when a clinician has at least a moderate suspicion of HIT that heparin administration from any source be terminated. This includes exposure to LMWH, heparin-coated catheters, and heparin flushes (6,30). If warfarin therapy has been started when HIT

is diagnosed, reversal with vitamin K should occur because of its depletion of proteins C and S and the increased risk for venous limb gangrene (6,77). Warfarin also increases the activated partial thromboplastin time (aPTT) and can lead to underdosing of the selected direct thrombin inhibitor (DTI) for treatment (78).

Although rare and controversial, fondaparinux has also been reported to create a similar clinical condition to that of HIT; conversely, it has also been studied as a treatment alternative (79–82).

Cessation alone is not enough to prevent thrombotic events. The 30-day risk for subsequent thrombosis following the cessation of heparin therapy is estimated to be at least 19% and possibly as high as 52% (83–85). This emphasizes the importance of beginning rapid-acting, alternate anticoagulation to reduce the heightened thrombin production and lessen the risk for thromboembolism.

PLATELET TRANSFUSION. Although it may seem intuitive to transfuse platelets to patients with HIT to control bleeding or for prophylaxis secondary to thrombocytopenia, treatment guidelines prior to 2010 warned against platelet transfusion. From 1970 to 2010, several different case series provided varying results. Whereas earlier studies demonstrate a lack of sustained platelet count and an increased risk for thrombosis, the latter case series concluded the opposite to be true (86–89).

Because of the limited evidence available, the 2012 American College of Chest Physicians (ACCP) guidelines do not recommend routine platelet transfusion in patients with HIT. However, they do support transfusions to severely thrombocytopenic patients with HIT who are bleeding or necessitate transfusion during the performance of an invasive procedure with a high risk for bleeding (6). More recently, Goel et al. (90) further stratified the risk for platelet transfusion by using the Nationwide Inpatient Sample registry, producing results from the largest available inpatient database. Among those diagnosed with HIT, 7.1% received platelet transfusions; 20.6% of these patients experienced thrombotic complications, revealing a significant association between platelet transfusions and arterial thrombotic events in HIT.

ALTERNATIVE ANTICOAGULATION. Recommendations for alternative anticoagulation are for patients whose diagnoses have been confirmed by laboratory results (in addition to the appropriate clinical context) or have a high suspicion for HIT on the basis of clinical evaluation alone. It is important to remember that HIT can cause an increase in aPTT, international normalized ratio (INR), and activated clotting time (ACT); thus, baseline laboratory values should be obtained to avoid confounding and subsequent treatment failure (91).

The alternative agents must be immediate acting and capable of interrupting the activated coagulation cascade at the level of thrombin or factor Xa (92). Therapy for HIT needs to be individualized and based on several important aspects, most notably the type of patient (cardiovascular, orthopedic, and so on), organ function, the likelihood of additional procedures, and bleeding risk (93,94). The 2012 ACCP clinical guidelines recommend treating HIT and HITT with the nonheparin anticoagulant agents lepirudin, argatroban, and danaparoid (6). Of those 3, only the DTI argatroban is approved by the U.S. Food and Drug Administration (FDA). The antifactor Xa danaparoid is not used for treatment in the United States, and lepirudin is no longer manufactured. Bivalirudin is not currently approved for treatment of HIT, but several studies have investigated its potential (95–97). Finally, although novel oral anticoagulant agents (rivaroxaban, dabigatran, and apixaban) are being investigated, there are no current guidelines for their use in the treatment of HIT or HITT.

Alternative anticoagulation in patients with HIT should not include either LMWH or warfarin, as both can worsen the thrombin generation and risk for thrombosis (6,77). Moreover, LMWH's cross-reactivity with HIT antibodies is quite significant and can approach 90% (98,99).

ARGATROBAN. Basic characteristics. Argatroban is a synthetic DTI that reversibly binds to thrombin and does not require AT3 for its activity. Currently, it is approved for prophylaxis or treatment of thrombosis in patients with HIT or as an anticoagulant agent during percutaneous coronary intervention (PCI) when heparin is contraindicated (92,100–103).

Initiating an argatroban infusion produces immediate anticoagulant effects as increasing plasma concentrations are obtained. Steady-state levels usually occur within 1 to 3 h and are maintained until the infusion is discontinued or the dose is adjusted. Argatroban exerts its anticoagulant effects by inhibiting thrombin-catalyzed or induced reactions, including fibrin formation, activation of coagulation factors V, VIII, and XIII, activation of protein C, and platelet aggregation. In addition, argatroban is capable of inhibiting the action of both free and clot-bound thrombin (92,100,102–104).

Pharmacokinetics. Unlike several other DTIs, the clearance of argatroban primarily consists of hepatic metabolism with biliary excretion and does not require dose adjustment in renal failure. The half-life

of argatroban in patients without hepatic impairment is 40 to 50 min (4,101,102,104).

DOSING. For prophylaxis or treatment of thrombosis in HIT, the prescribing information for argatroban recommends an initial infusion of 2 μg/kg/min, and it is advised to obtain a baseline aPTT before beginning therapy. An initial dose of 0.5 μg/kg/min is recommended for patients with moderate to severe hepatic impairment and HIT, but obtaining an acceptable aPTT may take longer and require more dose adjustments (100,103). A reduced dose should be considered in patients with heart failure, multiple-organ system failure, severe anasarca, or who are post-cardiac surgery. It is suggested to begin the initial infusion rate between 0.5 and 1.2 μg/kg/min, with subsequent adjustments every 2 h using the aPTT (**Table 3**) (6,104).

Although argatroban showed promising results as an anticoagulant agent in patients with HIT or HITT requiring PCI (105), it is not commonly used by practitioners, and dosing instructions will thus not be reviewed here.

Monitoring. Argatroban prolongs prothrombin time, aPTT, and ACT; both aPTT and ACT are useful point-of-care tools for monitoring the impact of argatroban anticoagulation (6,40,100,101). For use in HIT, a target range of 1.5 to 3 times the initial aPTT (not to exceed 100 s) is required, and steady-state levels are typically obtained within 1 to 3 h (**Table 3**).

BIVALIRUDIN. Basic characteristics. Bivalirudin is a DTI that is effective on both free and clot-bound thrombin and does not bind to other plasma proteins. Structurally, it is a synthetic hirudin analogue, but with less immunogenicity and reliance on renal clearance than hirudin. Unlike heparin, which is reliant on antithrombin (AT3) concentration, bivalirudin does not need a cofactor to function. In addition, bivalirudin inhibits platelet activation and adhesion by decreasing circulating von Willebrand factor and by directly attenuating thrombin's receptor-mediated activation of platelets (106).

TABLE 3 Dosage and Monitoring of Argatroban for Patients With HIT or HITT (103,142)

	Infusion Rate (μg/kg/min)*	Monitoring
Normal organ function	2	Until steady-state aPTT is 1.5–3 times baseline‡§
Hepatic impairment (total serum bilirubin >1.5 mg/dl)	0.5†	
Heart failure Multiple organ system failure Anasarca Post-cardiac surgery	0.5–1.2	

*Not to exceed 10 μg/kg/min. †Steady-state aPTT may take longer and require more dose adjustments. ‡aPTT drawn 2 h after initial bolus dose and after any dose adjustments. §Not to exceed 100 s.

aPTT = activated partial thromboplastin time; HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia with thrombosis.

Specifically, bivalirudin is FDA approved for use during PCI and percutaneous transluminal coronary angioplasty in patients with acute or previous HIT and in patients with HITT. Although not approved for the treatment of HIT, several retrospective studies have evaluated its therapeutic role in this patient population and support it as a possible alternative (95–97). However, when comparing bivalirudin and argatroban, Skrupky et al. (95) found the incidence of new thromboembolic events to be 2-fold higher in their patients receiving bivalirudin (8% vs. 4%); bleeding events occurred at similar rates for both groups.

Recent small, single-center, retrospective analyses by Vo et al. (107) and Bain and Meyer (108) suggest that bivalirudin appears to be able to reach therapeutic aPTT values quicker, maintain its therapeutic levels more consistently, and achieve similar outcomes compared with argatroban in patients with HIT. Furthermore, in the largest retrospective series to date, Joseph et al. (109) reiterated the positive results from previous studies, thus supporting the need for further research into bivalirudin's safety and efficacy for the treatment of HIT.

Pharmacokinetics. Bivalirudin exhibits linear pharmacokinetics and, as mentioned previously, does not bind to plasma proteins other than thrombin. The binding of thrombin to bivalirudin is temporary, because of the proteolytic action of thrombin itself on the shared bond; this is the major component of bivalirudin's clearance. A lesser component of renal excretion exists, which accounts for approximately 20% of the drug's clearance (110,111).

Drug elimination is relative to glomerular filtration rate (and independent of dose and sex); thus, the 25- to 30-min half-life in a healthy patient is extended to 1 h in severe renal disease and to 3.5 h in end-stage renal disease requiring hemodialysis (110,112). In addition, approximately 25% can be cleared by hemodialysis (111).

Monitoring. The response to a dose of bivalirudin is reflected with linear increases in prothrombin time, aPTT, ACT, and thrombin time (113,114). ACT tends to be less precise at high concentrations of bivalirudin (such as may be used for anticoagulation for CPB). The less commonly available ecarin clotting time (ECT) point-of-care test is recommended for intraoperative monitoring during CPB with bivalirudin (110). The ECT test uses ecarin to produce

meizothrombin when mixed with prothrombin and can be used to quantify the effect of DTIs (115).

Dosing. The recommended dose of bivalirudin in patients with HIT or HITT undergoing PCI begins with a bolus of 0.75 mg/kg, followed by a continuous infusion at 1.75 mg/kg/h for the entire length of the procedure. If ongoing treatment is needed post-procedure, the infusion may be continued for up to 4 h and then decreased to 0.2 mg/kg/h for up to 20 h. Patients with renal impairment will need dosage adjustments on the basis of their creatinine clearance, as the half-life increases with worsening function. See **Table 4** for dosing recommended by the manufacturer; note that there is no reduction in the bolus dose for any degree of renal impairment (111).

Proposed bivalirudin dosing for the medical treatment of HIT and HITT is different from the established PCI dosing guidelines discussed previously. Infusion rates range from 0.05 to 0.2 mg/kg/h in patients with normal renal function. Patients with renal dysfunction or hepatic dysfunction and those in an intensive care setting require lower doses to achieve appropriate aPTT values (1.5 to 2.5 times baseline). Bivalirudin has been started at 0.14 mg/kg/h in patients with hepatic dysfunction, 0.03 to 0.05 mg/kg/h in those with renal or combined hepatic and renal dysfunction, and 0.03 to 0.04 mg/kg/h in patients receiving continuous renal replacement therapy (10,95,96,109,116,117).

FONDAPARINUX. Fondaparinux increases the ability of antithrombin to inactivate factor Xa. It does not bind to or interact with other plasma proteins, is eliminated mostly unchanged in the urine (up to 80%), and has a half-life of 15 to 17 h (up to 21 h in older patients). In addition, steady-state plasma levels are achieved after the third or fourth once-daily dose (118,119). Monitoring is usually unnecessary during therapy, thus offering a major advantage over other anticoagulant agents and avoiding the issue of confounding discussed earlier (43).

In the most recent ACCP guidelines, HIT and HITT therapy with fondaparinux was not recommended, because of a lack of non-case-report-based evidence (6). As previously mentioned, fondaparinux has been implicated as a causative agent of HIT. However, additional studies have shown effective results and minimal cross-reactivity with HIT serum, making it an unlikely precipitating agent (27,120–122). In a recent retrospective, propensity-matched study by Kang et al. (123), fondaparinux had similar effectiveness and safety as argatroban and danaparoid in patients with suspected HIT. To date, this is the largest study providing evidence for the use of fondaparinux. Although there are several possible limitations to this study, it certainly supports the need for further investigation into fondaparinux's role in HIT treatment.

TABLE 4 Bivalirudin for PCI in HIT and HITT (111)

CrCl (ml/min)	Bolus Dose (mg/kg)	Infusion Dose (mg/kg/h)
≥90	0.75	1.75
30-59	0.75	1.75
<30	0.75	1
Hemodialysis	0.75	0.25

CrCl = creatinine clearance; PCI = percutaneous coronary intervention; other abbreviations as in **Table 3**.

PLASMAPHERESIS. Research into the use of plasmapheresis in patients with HIT or HITT began in the late 1980s, when reports showed favorable outcomes for both pretreatment before CPB and treatment for thrombosis (124–126). Since then, several other investigators have published similar results for both respective clinical scenarios: adjunctive treatment to remove IgG antibodies before CPB (127–131) and those with HITT (132–136). Interestingly, in a randomized controlled study performed in 1999, Robinson et al. (137) showed decreased mortality in HIT patients when treated within 4 days of the onset of thrombocytopenia.

Nonetheless, in the most recent guidelines by the American Society of Apheresis, therapeutic plasma exchange is a grade 2c recommendation for treatment of patients with HIT (pre-CPB and HITT) (138). Furthermore, the updated ACCP guidelines do not discuss the use of plasmapheresis for treatment of patients with HIT, regardless of the clinical scenario (6). Despite this, interest in the use of plasmapheresis continues; most recently, it was shown to alleviate clinical symptoms and reduce thrombotic risk in an HIT patient with intracerebral hemorrhage (139).

CONVERSION TO ORAL ANTICOAGULANT THERAPY. According to the ACCP guidelines, a transition to warfarin therapy is required for 3 months in patients with HITT and 4 weeks in those with isolated HIT. The guidelines also recommend delaying the initiation of therapy until the platelet count has recovered to at least 150×10^9/l, because concurrent thrombocytopenia may reflect the ongoing prothrombotic state of HIT (6). However, as there is no direct evidence to support a particular platelet threshold to begin therapy, some clinicians advocate beginning treatment as soon as the platelet count begins to rise (140).

Further evidence suggests an association between warfarin therapy in patients with HIT and venous

TABLE 5 Trials Evaluating the Use of Bivalirudin in Cardiac Surgery

First Author (Study) (Ref. #)	Design	Surgery	Population	Comparator	Outcomes Studied	Results With Bivalirudin (vs. Heparin)	Bleeding Rates*	Mortality	Q-Wave Myocardial Infarction
Merry et al. (154)	Multicenter, randomized unblinded, prospective	OPCAB	100 patients without HIT	Bivalirudin vs. UFH with protamine reversal	Blood loss, graft flow at 3 months	No significant increase in blood loss, superior graft flow	UFH: 805 ml (IQR: 517–1,117 ml) Bivalirudin: 793 ml (IQR 320–4,909 ml) p = 0.165	UFH: 30-day: 0 of 50 Bivalirudin: 30-day: 1 of 50	UFH: 7 of 50 Bivalirudin: 8 of 50
Dyke et al. (EVOLUTION-ON) (156)	Multicenter, 2:1 randomized, unblinded, prospective	CPB for primary or reoperation CABG or valve	150 patients without HIT	Bivalirudin (n = 98) vs. UFH with protamine reversal (n = 52)	Mortality, bleeding, myocardial infarction, stroke, need for repeat revascularization	No significant differences in composite outcome seen at 7 days (95% vs. 96%), 30 d (95% vs. 94%), 12 week (95% vs. 92%)	UFH: 668 ml Bivalirudin: 793 ml p = 0.0009	UFH: 30-day: 1 of 52 12-week: 2 of 52 Bivalirudin: 30-day: 3 of 52 12-week: 3 of 52	UFH: 7-day: 1 of 52 30-day: 1 of 52 12-week: 1 of 52 Bivalirudin: 7-day: 1 of 98 30-day: 1 of 98 12-week: 1 of 98
Smedira et al. (EVOLUTION-OFF) (157)	Multicenter, 2:1 randomized, unblinded, prospective	OPCAB	157 patients without HIT	Bivalirudin (101 patients) vs. UFH with protamine reversal (n = 56)	Mortality, bleeding, myocardial infarction, need for repeat revascularization	No significant differences in composite outcome seen at 7 days (96% vs. 95%), 30 days (93% vs. 93%), 12 weeks (93% vs. 93%)	UFH: 783 ml (IQR: 528–1,032 ml) Bivalirudin: 717 ml (IQR: 475–1,190 ml)	UFH: 7-day: 1 of 56 30-day: 1 of 56 12-week:1 of 56 Bivalirudin: 7-day: 1 of 101 30-day: 2 of 101 12-week: 2 of 101	UFH: 7-day: 0 of 56 30-day: 0 of 56 12-week: 0 of 56 Bivalirudin: 7-day: 2 of 101 30-day: 2 of 101 12-week: 2 of 101
Koster et al. (CHOOSE-ON) (42)	Multicenter, prospective	CPB for primary or reoperation CABG or valve	49 patients with confirmed HIT	None	Mortality, myocardial infarction, stroke, need for repeat revascularization	Composite outcome seen at 7 days (94%), 30 days (86%), 12 weeks (82%)	Bivalirudin: 998 ± 598 ml	7-day: 1 of 49 30-day: 3 of 49 12-week: 3 of 49	7-day: 0 of 49 30-day: 0 of 49 12-week: 0 of 49
Dyke et al. (CHOOSE-OFF) (155)	Multicenter, prospective	OPCAB	51 patients with confirmed HIT	None	Mortality, myocardial infarction, stroke, need for repeat revascularization	Composite outcome seen at 7 days (92%), 30 days (88%), 12 weeks (88%)	Bivalirudin: 926 ± 525 ml	7-day: 0 of 51 30-day: 0 of 51 12-week: 0 of 51	7-day: 3 of 51 30-day: 5 of 51 12-week: 5 of 51

*All bleeding rates are for 24-h period, except for Merry et al. (12-h bleeding rates).

CABG = coronary artery bypass graft; OPCAB = off-pump coronary bypass procedure; IQR = interquartile range; UFH = unfractionated heparin; other abbreviations as in Table 1.

limb gangrene; these patients commonly present with supratherapeutic INRs from the severe protein C depletion (6,141). Thus, premature cessation of a nonheparin anticoagulant agent before the therapeutic effect of warfarin occurs can increase the risk for a new thrombotic event. It is critical to overlap the nonheparin anticoagulant agent with warfarin for at least 5 days to safely reduce the prothrombin levels and to begin treatment at low doses (≤5 mg) to avoid complications (6).

Finally, clinicians must specifically recognize the cumulative effect of argatroban and warfarin on INR when transitioning to oral anticoagulation and should consult their institutions for using INR as an indicator of effect. Recommendations for overlapping therapy, depending on the dose of argatroban, include stopping argatroban when the INR is >4, waiting 4 to 6 h, and continuing therapy with warfarin alone if the INR is within the desired therapeutic range (103,142). Some experts also suggest the alternative option of transitioning from argatroban to fondaparinux, which has a minimal effect on INR (6).

REEXPOSURE TO HEPARIN. Typically, the heparin-dependent antibodies fall to undetectable levels after 50 to 85 days (35). Thus, once antibodies are no longer present, the AACP guidelines recommend the (short-term) use of heparin for cardiac surgery patients with histories of HIT. However, for patients with histories of HIT undergoing PCI, the recommendation is to use a nonheparin anticoagulant agent (6).

TABLE 6 Bivalirudin Protocol

General Guidelines
• Advance communication and planning with perfusion and surgery are critical.
• Anesthesia staff should calculate in advance the likely amount of bivalirudin that will be required for the case and obtain it from the pharmacy.
• All flush solutions, lines, and cell saver must be prepared with bivalirudin (0.1 mg/ml; 1 ml for every 5 ml cell saver processed) instead of heparin.
• The bivalirudin is supplied as 250 mg/vial and is typically prepared as 250 mg in 50 ml (although 500 mg in 100 ml is probably more convenient).
Dosing
Initial bivalirudin load
• 1.25 mg/kg load over 5 min
• 50 mg in pump prime
Maintenance
• 2.5 mg/kg/h infusion (42 μg/kg/min)
• Use a dedicated line through a separate pump.
Monitoring
• Keep kaolin ACT >500 s (or at least 2.5 times baseline).
◦ If <500 s, bolus 0.25 mg/kg and increase infusion by 0.25 mg/kg/h.
• Avoid circulatory stasis. Use recirculation limbs and keep cardioplegia circulating if containing blood. Avoid hemofiltration during CPB to avoid removal of bivalirudin.
Management at the end of CPB
• Careful consideration of the likely success of separation from CPB is necessary, and the anesthesia, perfusion, and surgical teams should agree upon the strategy for termination of the bivalirudin infusion.
• Stop infusion 10–15 min before weaning from CPB and then either:
◦ Empty pump into the cell saver system to remove bivalirudin and replace with crystalloid.
◦ Add 50 mg bivalirudin to the pump circuit, keep the blood recirculating (may require a cross limb bridge between the venous and arterial lines), and initiate 50 mg/h infusion into the bypass circuit, which should be continued until such time as it is clear that the patient will not require urgent return to CPB.
• Ultrafiltration by the perfusionist can remove approximately 70% of the bivalirudin from the patient.
If separation from CPB does not occur within 20 min of stopping infusion, redose patient with 0.5 mg/kg and restart infusion at 2.5 mg/kg/h.

ACT = activated clotting time; CPB = cardiopulmonary bypass.

HIT AND CPB

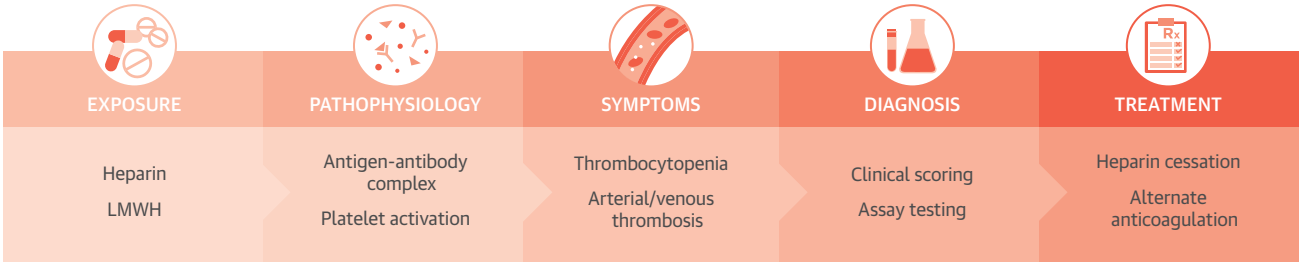
A patient with HIT who requires cardiac surgery is a particular challenge, requiring a team approach to provide optimal care (4,143). UFH is the gold standard anticoagulant for CPB, but patients with HIT may need to be administered alternative drugs (14).

Patients requiring cardiac surgery with histories of HIT >100 days prior should have serologic testing, as HIT antibodies are transient and generally become nondetectable within 50 to 85 days (35). If antibody is undetectable and platelet count has recovered, the ACCP recommendation is that patients can be safely re-exposed to heparin during cardiac surgery (4,41,144–146). Although studies indicate that there is no amnestic immune response (35,147), these patients should be closely monitored for thrombocytopenia in the post-operative period, with a low threshold for prophylactic use of alternative anticoagulation (11). Furthermore, heparin use should be limited to the procedure, with alternative anticoagulant agents used perioperatively (4,6,16).

However, in patients with subacute (detectable antibody and normal platelet counts) or acute HIT (antibody plus thrombocytopenia), re-exposure to heparin must be avoided, and an alternative strategy for anticoagulation is needed. The safety profiles of these alternatives are not well studied, and there are no known reversal agents (148), so all attempts to delay the surgery should be made (4,6,41).

For patients requiring cardiac surgery, past options have included an alternative anticoagulant agent (bivalirudin or argatroban), combining UFH with a platelet antagonist (epoprostenol, iloprost, or tirofiban), or the use of plasmapheresis (4,128,143,149–152). Although it is still not FDA approved for use in CPB (6,14), the ACCP recommendation is to use the DTI bivalirudin for the procedure and postoperative period, because of the evidence demonstrating its usefulness and safety compared with other DTIs (4,6,11,153). Bivalirudin has been shown in 5 randomized trials for both on-pump and

CENTRAL ILLUSTRATION **Heparin-Induced Thrombocytopenia: From Exposure to Treatment**



Salter, B.S. et al. J Am Coll Cardiol. 2016;67(21):2519–32.

LMWH = low-molecular weight heparin.

off-pump cardiac surgery to be a feasible alternative to heparin, without significantly increased mortality or morbidity, including bleeding (**Table 5**) (42,154–157).

Although ECT is recommended for intraoperative monitoring, because it is not widely available, ACT can be used as a safe alternative, with bivalirudin producing a linear dose-response anticoagulant effect (15,42). A target plasma drug level of 10 to 15 μg/ml should be achieved at the start of CPB, which corresponds to an ECT of 400 to 500 s or an ACT >500 s (14,158). Approximately 4 to 5 half-lives are needed for the effects of bivalirudin to be eliminated, unless their elimination is accelerated by hemodialysis or extracorporeal hemofiltration (148,159,160). A treatment protocol for bivalirudin anticoagulation during CPB is in **Table 6**.

Other areas of importance in regard to HIT and CPB include blood stasis and temperature management. It is critical to avoid blood stasis during CPB (4), because this allows bivalirudin metabolism to continue, increasing the risk for thrombus formation because of decreasing local bivalirudin levels, despite the presence of adequate systemic levels (148,161).

In addition, hypothermia reduces the proteolysis of bivalirudin; therefore, the patient's core temperature should be maintained close to 37°C following separation from CPB, and care should be taken to maintain body temperature during the early postoperative period (4).

HIT AND THE CATHETERIZATION LABORATORY

Argatroban, lepirudin, and bivalirudin have all been FDA approved as antithrombotic agents for patients with HIT requiring PCI, but the ACCP recommends the use of bivalirudin or argatroban (6,11). This recommendation was based on pooled data from multiple randomized trials (>19,000 patients without HIT) that demonstrated the efficacy and safety of bivalirudin anticoagulation during PCI, with a similar incidence of ischemic complications and a reduction in bleeding compared with UFH (6,162–167). Although more recent clinical trials (168–170) have also shown a similar or lower bleeding risk with bivalirudin (compared with UFH plus a glycoprotein IIb/IIIa receptor inhibitor or UFH alone), they demonstrated a significantly increased risk for stent thrombosis. In light of these new data that call into question the clinical utility and cost-effectiveness of bivalirudin in PCI, its use in patients without HIT has been questioned (168). However, in patients with HIT, bivalirudin remains the best option (6).

CONCLUSIONS

HIT is a rare complication seen in patients receiving anticoagulation therapy with heparin. Because of the high morbidity and mortality of this condition, it is paramount that all physicians managing these patients be aware that thrombocytopenia can represent an early warning sign mandating further workup to exclude HIT as a possible etiology (**Central Illustration**). With vigilance and an elevated degree of suspicion, the diagnosis can be confirmed while still in the early phase of the condition, and appropriate alternative anticoagulation therapies started, resulting in reduction of morbidly and mortality.

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